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# TSC Alliance Innovation Workshop Grant

## Newborn Screening Assay Development

2021 | Total Funding Available: \$200,000

### BACKGROUND

#### Tuberous sclerosis complex

Tuberous sclerosis complex (TSC) is a multisystem autosomal dominant genetic disorder that causes non-malignant tumors in vital organs including the brain, eyes, heart, kidneys, liver, skin, and lungs. In addition to tumor growth, neurological and neuropsychological manifestations such as epilepsy, intellectual disability, and autism can be devastating, requiring lifelong assistance for those affected.

The incidence of TSC is estimated at 1 in 6,000-10,000 live births<sup>1,2</sup>. Given this, approximately two children born each day in the United States will have TSC. Although some signs of TSC can be identified *in utero* or at birth, most infants born with TSC are not identified at birth<sup>3</sup>.

TSC is caused by a mutation in either the *TSC1* or *TSC2* gene. Two-thirds of individuals with TSC are born into families with no prior history of TSC due to a sporadic mutation in one of the TSC genes occurring in the parents' egg or sperm cell, or early in embryonic development<sup>4</sup>. Only one-third of individuals with TSC are born into a family with TSC.

TSC1 and TSC2 proteins (hamartin and tuberlin, respectively) form a complex that negatively regulates mTOR (mechanistic target of rapamycin), a key regulator of cell growth, size, and metabolism that leads to tumor growth and cellular dysfunction. Fortunately, mTOR inhibitor therapies (sirolimus and everolimus) have proven effective at reducing tumor burden and epilepsy severity. Current clinical trials including STOP-2 (Stopping TSC Onset and Progression 2, [NCT04595513](https://clinicaltrials.gov/ct2/show/study/NCT04595513)) and PREVeNT (Preventing Epilepsy Using Vigabatrin in Infants with TSC, [NCT02849457](https://clinicaltrials.gov/ct2/show/study/NCT02849457)) are evaluating the effectiveness of preventative treatment with sirolimus and vigabatrin, respectively, to prevent the onset of seizures and/or the developmental delay due to epilepsy in TSC infants.

Hope no matter how complex

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## Why the need for early detection?

Early detection and diagnosis of TSC in infants provides a unique opportunity to intervene early with therapeutics to alter the course of TSC development or onset of its many manifestations, including epilepsy. Unfortunately, since two-thirds of new cases of TSC are due to spontaneous or new mutations, diagnosis often occurs after the onset of epilepsy, and an accurate diagnosis is often delayed due to the heterogeneous presentation of the manifestations. If the PREVeNT and STOP-2 trials demonstrate the superior effectiveness of treatment prior to onset of seizures to prevent epilepsy and developmental delay, they will justify newborn screening (NBS) for TSC.

## INNOVATION WORKSHOP RECOMMENDATIONS

A virtual Innovation Workshop on newborn screening for TSC was held using Zoom and Pownoodle in late 2020, culminating in a Zoom meeting on January 29, 2021. Participants included 20 researchers with TSC expertise; 19 researchers with NBS experience from CDC, NIH, and academic laboratories; and 5 representatives of non-TSC advocacy organizations with NBS experience.

A major goal of the workshop was to recommend how best the TSC Alliance should invest \$200,000 to stimulate research toward development of an assay to identify newborns with TSC. The recommendations were:

1. Because most NBS assays used today measure metabolites or other analytes in blood, the TSC Alliance should fund research to identify a biomarker (e.g., metabolite or protein) or a panel of biomarkers which may be unique for TSC in dried blood spots from infants. Future funding and work would be required to develop a specific assay for the candidate biomarker(s).
2. Because TSC is an autosomal dominant disease and most pathogenic variants in *TSC1* and *TSC2* are truncating mutations or deletions, and because many other variants likely lead to loss of protein, the TSC Alliance should fund research to test the viability of an assay to detect a 50% decrease of hamartin or tuberin in blood of infants with TSC.

Workshop participants recognized that other scientists may have additional viable approaches toward a TSC NBS assay, but participants discouraged genetic sequencing as an approach due to cost. Also, the workshop participants recommended the TSC Alliance find or acquire resources necessary to support the funded research, such as cord blood and dried blood spots from individuals with and without TSC.

## PROGRAM GOAL

The *ultimate* goal of the TSC Alliance's newborn screening efforts is to identify and develop a newborn screening assay for TSC suitable for inclusion in the Recommended Uniform Screening Panel (RUSP) for NBS<sup>5</sup>. Currently, most NBS assays on the RUSP utilize tandem mass spectrometry (MS) to detect metabolites or other analytes. Because NBS is administered and paid for by state governments and will be performed on four million newborns per year in the United States, the test should utilize dried blood spots and be very inexpensive (pennies per assay). For this reason, a TSC NBS assay which can be multiplexed with existing NBS assays is strongly preferred.

The goal of this funding opportunity announcement (FOA) is to take the first steps to identify a biomarker (or combination of biomarkers) for TSC detectable in dried blood spots from infants through targeted (hypothesis-driven) experiments or non-targeted metabolomic or proteomic profiling. Because this FOA is funding only the first steps, the proposed research may utilize, but is not required to utilize, dried blood spots. However, the approach should ultimately be adaptable to dried blood spots with additional work.

## RESOURCES AVAILABLE

The TSC Alliance is providing a [Newborn Screening Toolkit](#) of biosamples available in the TSC Biosample Repository and other resources of which we are aware. If you know of additional relevant resources we should include, please email us at [biosample@tscalliance.org](mailto:biosample@tscalliance.org) and we will update the toolkit.

The TSC Alliance will work with awardees to provide samples from the TSC Biosample Repository through a separate, brief application and material transfer agreement (MTA). Additionally, any researcher, whether funded through this FOA or not, may request biosamples for TSC-related research at any time. Please email [biosample@tscalliance.org](mailto:biosample@tscalliance.org) for more information.

## PROGRAM PRIORITIES

**Applications must address one of the two recommendations from the Innovation Workshop** or, if proposing an alternative approach, the application must justify the rationale for an alternative approach, and the applicant should discuss the idea with TSC Alliance staff in advance.

1. Research (e.g., metabolomics or proteomics) to identify a biomarker or a panel of biomarkers which may be unique for TSC in dried blood spots from infants, recognizing that future funding and work would be required to develop a specific assay for the candidate biomarker(s).
2. Research to develop and test the viability of an assay to detect a 50% decrease of hamartin or tuberin in blood of infants with TSC.

Unless the applicant can demonstrate compatibility with existing NBS technology in use by states, genetic sequencing or other genetic approaches will not be funded.

TSC Alliance Innovation Workshop Grants support research that aims to address the Program Priorities in this FOA and are not intended to act as a funding stream to continue the projects previously supported by the TSC Alliance.

## PROCESS AND KEY DATES

A Letter of Intent (LOI) is required; however, the LOI will be used for TSC Alliance's planning purposes only (e.g., identifying reviewers) and will not be peer-reviewed. TSC Alliance staff will contact an applicant if staff have questions about the relevance of the proposed research to the Program Priorities.

LOIs and Applications will only be accepted through the online submission system ([Proposal Central](#)).

Applications will be evaluated by reviewers identified by the TSC Alliance, including experts selected from the International Scientific Advisory board or *ad hoc* reviewers who will evaluate applications for rationale, aims, research strategy and feasibility, and

potential impact on the Program Priorities. Appropriateness of the budget will be evaluated but not scored.

**Online portal opens:** July 16, 2021

**Letter of Intent (LOI) Due:** August 23, 2021

**Applications Due:** September 13, 2021

**Award Start Date:** December 1, 2021

## AWARD INFORMATION

**Duration:** Maximum of 12 months, but the duration may be for a shorter period if appropriate to the proposed research.

**Total to be Awarded in Response to this FOA:** \$200,000

**Individual Award Budget:** \$10,000 to \$150,000.

Applicants are encouraged **not** to apply for the maximum amount—requested financial support must be commensurate with work proposed. For research including sequential or interdependent aims, milestones will be established, and subsequent funding will be dependent upon successful completion of the first aim(s). Final budgets and milestones will be negotiated based on review of the proposed work.

**Indirect Costs:** Budgets may include indirect costs up to a maximum of 10% of the award amount. For example, a \$50,000 award may include a maximum of \$5,000 indirect costs.

**Number of Awards Funded:** At the discretion of the TSC Alliance depending on the outcome of peer review and budget negotiations. No minimum or maximum number of awards is guaranteed.

## ELIGIBILITY REQUIREMENTS

This opportunity is open to investigators at established academic or research institutions or at pharmaceutical or biotech companies worldwide. Researchers residing in the United States do not need to be US citizens to apply for funding. Post-doctoral fellows are eligible to apply as co-investigators with the designation of an administrative primary investigator who directs the laboratory in which the fellow will conduct research. The administrative PI will be responsible for assisting in providing all institutional documents required for the project and will be required to sign any award contract. Training and mentoring-only proposals will not be considered.

As assay development programs may require many kinds of expertise, the TSC Alliance encourages industry and academic collaborations when appropriate.

## REQUIRED COMPONENTS OF THE LETTER OF INTENT (LOI)

1. Contact information of Principal Investigator (PI) and Key Personnel (i.e., collaborators), if applicable.
2. An [NIH-style biosketch](#) of the PI and any Key Personnel.
3. Estimated budget – this estimate is not binding but is helpful to TSC Alliance staff for planning.

4. A one-page description of the research to be proposed in the Application, addressing (1) how the research addresses the Program Priorities; (2) how the proposed research differs from known related research approaches in academia or industry; (3) on overview of the research strategy and predicted outcomes; and (4) potential impact and next steps.

## REQUIRED COMPONENTS OF THE APPLICATION

1. Contact information of Principal Investigator (PI) and Key Personnel (i.e., collaborators), if applicable, will be carried over from the LOI.
2. An [NIH-style biosketch](#) of the PI and any Key Personnel will be carried over from the LOI.
3. Budget details entered in the online template.
4. Budget justification uploaded as a PDF document, not to exceed one page.
5. A technical abstract not to exceed 2500 characters (including spaces) describing the proposed work, addressing: (1) how the research addresses the Program Priorities; (2) how the proposed research differs from known related research approaches in academia or industry; (3) on overview of the research strategy and predicted outcomes; and (4) potential impact and next steps.
6. Keywords selected from a list during the online application process.
7. A research plan of no more than 6 pages, including:
  - 7.1. Rationale – how the proposed innovation will make a difference (impact) and preliminary data to support the proposed aims.
  - 7.2. Aims – describe in technical detail the hypothesis and assumptions, explaining the proposed direction and the approach noting and why approach is compelling and likely to succeed.
  - 7.3. Research strategy – describe the experimental design and approach; include the type(s) of biological samples (e.g., peripheral blood, dried blood spots) that will be used and why, and include proposed biostatistical analyses.
  - 7.4. Timeline – identify detailed objectives and the anticipated timeline for achieving each aim, including any potential barriers to success and any interdependence between aims.
  - 7.5. Anticipated pathway for translation to TSC NBS assay – describe how the research will enable the development of a NBS assay for TSC, including next steps and potential funding opportunities for continuation.
  - 7.6. Technical contributions of Key Personnel
  - 7.7. References

## FOR INQUIRIES RELATED TO THIS FOA, CONTACT:

Zoë Fuchs, Science Project Coordinator: [zfuchs@tscalliance.org](mailto:zfuchs@tscalliance.org)

Steve Roberds, Chief Scientific Officer: [sroberds@tscalliance.org](mailto:sroberds@tscalliance.org)

## REFERENCES

<sup>1</sup>O'Callaghan FJK, Shiell AW, Osborne JP. Prevalence of tuberous sclerosis estimated by capture-recapture analysis. *Lancet* 1998;351:1490. [https://doi.org/10.1016/S0140-6736\(05\)78872-3](https://doi.org/10.1016/S0140-6736(05)78872-3).

<sup>2</sup>Ebrahimi-Fakhari D, Mann LL, Poryo M, Graf N, Von Kries R, Heinrich B, et al. Incidence of tuberous sclerosis and age at first diagnosis: new data and emerging trends from a national, prospective surveillance study. *Orphanet J Rare Dis* 2018;13. <https://doi.org/10.1186/s13023-018-0870-y>.

<sup>3</sup>Davis PE, Filip-Dhima R, Sideridis G, Peters JM, Au KS, Northrup H, Bebin EM, Wu JY, Krueger D, Sahin M and on behalf of the Tuberous Sclerosis Complex Autism Center of Excellence Research Network. *Pediatrics* 2017;140:e20164040. <https://doi.org/10.1542/peds.2016-4040>.

<sup>4</sup>Northrup H, Koenig MK, Pearson DA, Au KS. In: GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2021. 1999 Jul 13 [updated 2020 Apr 16]. <https://www.ncbi.nlm.nih.gov/books/NBK1220/>.

<sup>5</sup><https://www.hrsa.gov/advisory-committees/heritable-disorders/rusp/index.html>